Efficacy of intravenous paracetamol dilutions compared with lidocaine for prevention of propofol-induced pain during induction of anesthesia

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Received:10-02-2019, Revised:12-04-2019, Accepted: 14-05-2019

ABSTRACT

Background: Propofol is an intravenous anesthetic drug that is commonly used for induction of anesthesia; pain during induction of anesthesia with propofol is a common problem (with a prevalence of 28-90%) that can be distressful for patients. We aimed to compare the efficiency of intravenous paracetamol in different dilutions and lidocaine in prevention of propofol-induced pain.

Methods: In this randomized, double-blind clinical trial, 200 patients scheduled for elective surgery under general anesthesia with propofol was randomly assigned to 4 groups of 50 persons. In Group 1, 40 mg lidocaine in 5 ml normal saline; in group 2, 2 mg/kg Paracetamol in 5 ml normal saline; in group 3, 2 mg/kg Paracetamol in 20 ml normal saline, and in group 4, 5 ml normal saline were injected as control. Then, 25% of the calculated dose of Propofol (2.5 mg/kg) was injected at a speed of 0.5 ml/sec and the patient's pain was determined based on VRS score from 0-3. Then, general anesthesia was induced.

Results: In the four groups, there were no statistically significant differences in terms of age and sex. The amount of pain in Lidocaine group was significantly lower, compared to the control group (P=0.001), in the paracetamol group (P=0.03), in the diluted paracetamol group (P=0.009), but there was no significant difference among the three groups in terms of pain reduction.

Discussion: Both 2 mg/kg paracetamol in 5 ml normal saline and in 20 ml normal saline are as effective as 40 mg lidocaine in 5 ml normal saline.

Keywords: Paracetamol ; Lidocaine ; Propofol-induced pain

INTRODUCTION

Propofol is the most commonly used intravenous anesthetic drug (Abdo El Hamd et al., 2013). However, the induction of pain as the result of getting anesthetized with it is a common problem that can be agonizing for patients. The incidence rate of pain induced as the result of propofol injection has been reported up to 90% (Tan et al., 1998).

This pain relates to several mechanisms. The stimulation of the local kallikrein-kinin cascade pathway is one of them. Another proposed mechanism suggests the stimulation of nociceptors of the nerve endings in the intima and media layers of the veins' wall as the cause of pain.

Other proposed mechanisms are the concentration of propofol and PH (Kim et al., 2013). In order to decrease this pain, many interventions have been investigated such as addition of lidocaine to propofol (Kim et al., 2013; Jalota et al., 2011; Lee et al., 2010; Ahmad et al., 2013; Al Tariq, 2018).

Generally, pretreatment with 0.5 mg/kg intravenous (IV) lidocaine with vein occlusion is considered as the most effective interventional mechanism (Madenoglu et al., 2003; Kaya et al., 2006; Borazan et al., 2010; Heidary et al, 2017; Heidary&Riahi, 2018). Paracetamol is widely used to control pain in patients. Although its mechanism of action is not precisely known, its clinical effects are most probably the result of its central effect. Recent studies have also indicated that it has peripheral effects too which are the result of inhibiting the production of chemical receptors' impulses sensitive to bradykinin which are themselves responsible for the production of pain impulses (Schnider et al., 1998).

The proposed mechanisms lead to the investigation of the effects of IV paracetamol on propofol-induced pain.

Since some studies have shown that the dilution of lidocaine and increasing its volume can lead to further reduction of propofol-induced pain, we aim in this study to investigate the effect of paracetamol dilution on decreasing the level of pain in propofol-injected patients.

Materials and Methods

After obtaining permission from the Ethics Committee of the University and registration in the IRCT website (201604074131N1) , patients aged 20-60 years with ASA class I and II who were candidates of elective

surgery under general anesthesia at Imam Khomeini and Fatemi hospitals in Ardabil, were recruited into the study through convenient sampling after giving informed consent. Blinding was performed for the researcher and patients. Total sample size was calculated at 200 based on prevalence of propofol-induced pain and the sample size of previous studies, Patients were categorized into 4 groups of 50 patients, based on randomized blocks and the drugs were put in four bags. For all patients angiocatheter 20 was settled at the back of hand in theater room and 3-5 ml/kg serum was infused.

In Group 1, 40 mg lidocaine in 5 ml normal saline; in group 2, 2 mg/kg Paracetamol in 5 ml normal saline; in group 3, 2 mg/kg Paracetamol in 20 ml normal saline, and in group 4, 5 ml normal saline were injected as control. Before injection of the above drugs, 80 mmHg tourniquet was fastened on the arm that was kept for 3 minutes after the injection of drugs. Then, 25% of the calculated dose of propofol (2.5 mg/kg) was injected at a speed of 0.5 ml/sec and the patient's pain was determined based on verbal rating scale (VRS), scored from 0-3. The scoring system was as follows: score 0 (no pain) and 1 (mild pain) included pain in response to questions without behavioral symptoms; score 2 (moderate): pain associated with behavioral symptoms, score 3 (severe): severe audio response with frowning or pulling arms and tearing. Then, general anesthesia was induced. Data were analyzed by SPSS software version 21 and $p<0.05$ was considered statistically significant.

Results

Four groups did not have any significant differences with respect to the demographic characteristics (table 1).

Table 1. Comparison of demographic variables among four groups

Group	Group 1	Group 2	Group 3	Group 4	P-value
Variable	Lidocaine	Paracetamol	Diluted Paracetamol	Placebo	
Age (yrs)	35 ± 9.6	37.6 ± 10.5	35.6 ± 9.4	39.5 ± 12.3	0.230
Sex (male)	29 (58%)	25 (50%)	26 (52%)	17 (34%)	0.098
Weight	72.5 ± 14.9	75.1 ± 16.2	69.6 ± 13.2	76.2± 14.1	0.112
ASA Class (I)	42 (84%)	41 (82%)	44 (88%)	39 (78%)	0.606
Total dose of Propofolreceived by the patient (mg)	41.8 ± 6.3	43.6 ± 6.2	42.7± 6.6	40.4± 4.8	0.133

Four groups were compared in terms of pain-related factors using chi-square and ANOVA, including the pain onset, severity of pain based on VRS, and prevalence of swelling and redness at the injection site. The results of analysis showed that the 4 groups had no statistically significant difference regarding pain onset, and prevalence of swelling and redness at the injection site, but regarding the severity of pain, all 3 groups receiving lidocaine, paracetamol and diluted paracetamol had statistically significant difference with the control group, although the pairwise comparison showed no statistically significant between the 3 groups (table 2).

Table 2. Comparison of factors associated with propofol-induced pain in the study groups

Group	Group 1	Group 2	Group 3	Group 4	P- Value
Variable	Lidocaine	Paracetamol	Diluted Paracetamol	Placebo	
Pain onset	2.04 ± 3.64	1.91 ± 3.26	1.81 ± 2.50	1.09 ± 3.17	0.573
Pain severity based onmean VRS	0.9 ± 1.02	1.16 ± 1.05	1.06 ± 1.04	1.72 ± 1.01	0.001
Median	(Mild pain) 1	(Mild pain) 1	(Mild pain) 1	(Moderate pain) 2	-
Mode	0)Painless(	0)Painless(	0)Painless(	(Moderate pain) 2	-
Swelling and redness atthe injection site	3 (6%)	5 (10%)	4 (8%)	2 (4%)	0.792

Discussion

Propofol-induced pain is a major concern for anesthesiologists and patients, as it is classified as the seventh current major clinical problem of anesthesia (Schnider et al., 1998). The present study aimed to compare the efficacy of IV paracetamol in different volumes and lidocaine in prevention of pain during injection of propofol. The results of the study showed

that both 40 mg lidocaine in 5^{cc} normal saline, 2 mg/kg paracetamol in 5^{cc} normal saline, and 2 mg/kg paracetamol in 20^{cc} normal saline significantly decreased the pain of propofol injection (P=0.001), although the severity of pain in the lidocaine group was not lower than the two other groups and paracetamol group was not lower than the diluted group, no significant advantage was observed among the three groups in the reduction of propofol-induced pain.

In line with our findings, Khouadja et al. indicated that like lidocaine, intravenous paracetamol can also considerably reduce the propofol-induced pain (Khouadja et al., 2014).

It should be noted that they used a fixed dose of paracetamol (100 mg) for all patients in their study while we administered the drug with the dose of 2 mg/kg since the proportionality of the dose with the patients' weights might affect the level of pain reduction (Shabana et al., 2013).

The findings of the study conducted by Ozkan et al. are also consistent with our findings. They found that as was the case with lidocaine, the consumption of 100 mg acetaminophen considerably decreases the level of propofol-induced pain in patients using it compared to those in the control group (Ozkan et al., 2011).

Borazan et al.'sfindings are also consistent with our findings. They demonstrated in their study that the consumption of paracetamol with the doses of 0.5, 1, and 2 mg/kg considerably decreases the propofol-induced pain just as lidocaine with the dose of 0.5 mg/kg does. In their study, the effectiveness of paracetamol with the dose of 1 mg/kg was tantamount to that of lidocaine with the dose of 0.5 mg/kg, while paracetamol with the dose of 2 mg/kg showed the highest effectiveness (Borazan et al., 2011; Akar et al, 2018). The dose administered for patients in our study was also 2 mg/kg. Canbay et al. also reported similar findings. In their study too, the use of intravenous paracetamol caused a decrease in the level of propofol-induced pain just as lidocaine does (Canbay et al., 2008; Mostafavi et al, 2017).

In general, from among the various medications proposed for the reduction ofpropofol-induced pain, lidocaine is the most commonly used in clinics (Tarmiz et al., 2009).

The most common method used is addition of 10 to 40 mg of lidocaine to propofol syringe immediately before use, during which lidocaine reduced PH of the lipid emulsion of propofol that lead to decreased concentration of free propofol at the aqueous phase (Kim et al., 2010). However, to decrease propofol-induced pain, pretreatment with lidocaine was also used, like our study which is assumed to act as a local anesthetic (Khouadja et al., 2014).

Another drug used in our study was paracetamol, used as pretreatment before injection of propofol. The exact mechanism of action for numbness of paracetamol is not yet clear; its clinical efficacy is likely due to its central effects and the poor peripheral effects have recently gained considerable attention (Kim et al., 2010; Zarei&Roohafza, 2018).

Maybe, that is why the central analgesic effects of paracetamol are greater than its peripheral effects, thus, increasing the volume of paracetamol in our study had no significant effect on decreasing propofol-induced pain, compared to volume increase. Unlike our study, the study by Shabana and co-workers on the effect of diluted lidocaine (30 mg lidocaine with 20 ml normal saline before injection of propofol, compared with mixture of 30 mg lidocaine with propofol) on propofol-induced pain showed that using higher volumes of lidocaine significantly decreased propofol-induced pain than the control group (Shabana et al., 2013; Eissazadeh et al, 2019).

It is assumed that diluting and using higher volumes of lidocaine gives more opportunities to the drug to distribute in a larger pain area to block the nerve endings (Khouadja et al., 2014). In the present study, before injection of medicines, tourniquet was inflated with a pressure of 80 mmHg on the arm and kept fastened after injection for 3 minutes for all groups.

In a study conducted by Ozkan et al. patients in one group were administered 100 mg of paracetamol without tourniquet and those in the other group received the same dose of paracetamol together with a tourniquet (Ozkan et al., 2011). The results of their study indicated that although the use of paracetamol both with and without a tourniquet considerably decreases the level of pain in propofol-injected patients, this decrease is significantly more when paracetamol is used with a tourniquet. Sasaki et al. also reported that the analgesic effect of pre-injected lidocaine increases when a tourniquet is used simultaneously (Sasaki et al., 1999).

A meta-analysis by Picard and Tramer confirmed that lidocaine should be injected while using rubber tourniquet before injection of propofol for the highest analgesic efficacy (Picard &Tramer, 2000). Moreover, Kaya and co-workers also showed that pretreatment with lidocaine with venous occlusion for 60 seconds significantly reduced propofol-induced pain compared with lidocaine without venous occlusion (Kaya et al., 2006).

Mean pain onset in our patients was 1.65±3.14 seconds in the range of 0 to 20 seconds; there was also no significant difference among 4 groups in our study in terms of mean onset of pain. In general, propofol-induced pain has an initial component (due to immediate stimulation of pain receptors and free nerve endings) and a delayed component (caused by the production of bradykinin with activation of plasma calicrein-quinine system) and the delay component generally becomes apparent within 30 seconds after the injection (Sim et al., 2009).

Conclusions

In conclusion, the present results suggest that 2 mg/kg paracetamol in 5 ml normal saline and in 20 ml normal saline are as effective as 40 mg lidocaine in 5 ml normal saline. So, studies are required to determine the optimal doses of i.v. acetaminophen to control propofol-induced pain.

Conflict of interest: None declared.
Funding support: None.

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Acknowledgements
This article is taken from a student thesis at the Faculty of Medical Sciences, Ardabil - Iran. The authors would like to thanks subjects who willingly participated in the study.

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